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PRACTICE

EASILY MISSED?

Bladder cancer in women

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This is one of a series of occasional articles highlighting conditions that may be more common than many doctors realise or may be missed at first presentation. The series advisers are Anthony Harnden, university lecturer in general practice, Department of Primary Health Care, University of Oxford, and Richard Lehman, general practitioner, Banbury. To suggest a topic, please email us at practice@bmj.com

A 76 year old woman reports recurrent urinary frequency, dysuria, and malodorous urine. No bacterial growth has been identified on two midstream urine samples, though empirical treatment with antibiotics has improved her symptoms. After three months, an episode of visible haematuria prompts referral and a transitional cell carcinoma of the bladder is diagnosed.

What are the types of bladder cancer?

In developed countries 90% of bladder cancers are transitional cell carcinomas; squamous cell carcinomas (SCC) make up most of the remainder.[1 2] In endemic areas, squamous cell carcinoma related to schistosomiasis accounts for 70% of cases.[1] Around 20% are muscle invasive at diagnosis and are associated with a significantly poorer prognosis.[3] The major risk factor is smoking, though chronic infection, radiotherapy, and (before regulation) industrial dyes have been implicated.[2 4]

Why is it missed?

Although bladder cancer is more common in men, women experience more delays: the English National Audit of Cancer Diagnosis in Primary Care (2009-10) estimated that annually 435 more women than men with bladder cancer experience a delay in diagnosis, but there are few data from UK primary care to explain this.[6] With no effective screening tool for bladder cancer, it is usually diagnosed symptomatically, with haematuria being the most common presenting symptom for both sexes in primary care (likelihood ratio 59, 95% confidence interval 51 to 57).[3 7] The likelihood ratio summarises how many times more (or less) likely patients with bladder cancer are to have a particular feature than patients without bladder cancer. A ratio over 10 (or under 0.1) is considered to provide strong evidence to rule in (or rule out) bladder cancer.

A study of outpatient haematuria claims for 7649 patients aged >65 in the United States (female:male 1:2.43) also described a delay in diagnosis after presentation in women. The mean time to diagnosis was 85.5 days in women (95% confidence interval 81.3 to 89.4) compared with 73.6 days (71.2 to 76.1) in men (P<0.001). This difference persisted over time; women were 26% more likely to experience delay at three months after the initial claim, 16% at six months, and 23% at nine months.[8] During investigations, women undergo more urinalyses (1.39 *v* 1.19, P<0.001) and urine cultures (0.83 *v* 0.53, P<0.001) and receive more diagnoses of urinary tract infections (odds ratio 2.32, 95% confidence interval 2.07 to 2.59; P<0.001) and more antibiotics (40.1% *v* 35.4%, P<0.001), yet are less likely to undergo bladder imaging (odds ratio 0.80, 0.71 to 0.89; P<0.001).[8]

Bladder cancer is also associated with voiding disorders and abdominal pain, but European data from primary care and gynaecology report that women with these complaints are more likely to be treated empirically, with treatments given without further evaluation in 47% of women compared with 19% of men in the year before diagnosis (P<0.05).[9]

Although these data are not wholly derived from primary care, it is implicit that prolonged investigation and treatment for urinary tract infections over repeated consultations (without confirmation of symptom resolution) is more of a problem in women.

Why does this matter?

Although there are recognised sex differences in tumour biology, bladder anatomy, and environmental and hormonal exposures that contribute to differential outcomes, there is some evidence of a correlation between delay in primary care and worsening prognosis.[10-12]

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How common is bladder cancer in women?

- Bladder cancer is the seventh most common cancer in the United Kingdom and the 11th most common in women[5]
- In 2010 there were 10 324 new diagnoses of bladder cancer in the UK, with a female to male ratio of 2:5, accounting for 4900 deaths[5]
- An average general practice expects to see one new diagnosis of female bladder cancer every 3.5 years
- The average age at diagnosis is 71[5]

Prospective data from the UK for 1537 cases of bladder cancer (1340 detailing stage, and 633 both stage and cause of death) showed an association between longer delay between start of symptoms and GP referral and a 5% increased incidence of muscle invasive bladder cancer (pT2-4) (P=0.04).[12] Five year survival was significantly worse for women presenting with muscle invasive disease (P<0.001).[12] While the report did not distinguish between patient delay and GP delay, longer delay before referral (>14 *v* <14 days) resulted in an increased risk of death (hazard ratio 1.19, 95% confidence interval 1.01 to 1.42; P=0.04) and 5% poorer five year survival (P=0.02).[12] Patients with delay in their referral pathway seem to have more advanced disease, with poorer outcomes; arguably, they warrant the most expedient intervention compared with other groups.

How is it diagnosed?

Clinical features

The National Institute for Health and Care Excellence (NICE) recommends urgent urology referral for adults with visible haematuria in the absence of urinary tract infection or in the presence of recurrent or persistent urinary tract infection in those aged >40; for unexplained microscopic haematuria in those aged >50; and for an abdominal mass arising from the bladder; and a non-urgent referral in those aged <50 with unexplained microscopic haematuria without raised creatinine concentration or proteinuria.[13]

Most studies in primary care have examined haematuria alone, though two—which both used pre-existing medical records—reported a broad range of symptoms associated with bladder cancer per se[3] and with urinary tract cancer collectively.[14] Most patients presented with painless haematuria, voiding symptoms, or a combination of the two.

Haematuria

The case-control study using electronic medical records from UK primary care showed that painless macroscopic haematuria is the strongest predictor of bladder cancer in primary care (odds ratio 34, 95% confidence interval 29 to 41), with a positive predictive value in patients aged over 60 of 3.9% (3.5% to 4.6%).[3] The national audit showed that two thirds of patients had haematuria recorded as their primary symptom in primary care[6]; though the prospective secondary care study showed that 90% of referred patients had haematuria (the severity of which did not correlate with disease severity); 25% of those referred will have transitional cell carcinoma of the bladder.[6 12]

Less specific symptoms

The case-control study also showed that the commonly encountered symptoms of dysuria (odds ratio 4.1, 95% confidence interval 3.4 to 5.0), abdominal pain (2.0, 1.6 to 2.4), and constipation (1.5, 1.2 to 1.9), and a diagnosis of urinary tract infection (2.2, 2.0 to 2.5) are associated with bladder cancer but with much lower predictive values.[3] Patients with more advanced disease might present with pelvic pain or urinary obstruction. In these patients, a mass might be palpable. Importantly, re-attendance with persistent symptoms is associated with an increased risk of cancer.

Investigations

Non-specific

Urinalysis is accurate in detecting haematuria, proteinuria, nitrites, or leucocyte esterase, with subsequent microscopy and culture to confirm infection. Although three blood tests with abnormal results—raised white cell count, raised inflammatory markers, and raised creatinine—are associated with bladder cancer, these tests alone cannot be used to rule out the condition.[3] The main role of urine cytology is in follow-up of patients with carcinoma in situ, rather than in the diagnosis of cancer. No primary care studies have reported its performance characteristics in diagnosis, but sensitivity is only 38% in secondary care and probably lower in primary care.[15]

Definitive

Flexible cystoscopy is the mainstay of investigation and is performed on a day case basis. It allows direct visualisation and biopsy of bladder abnormalities, but not treatment. Ultrasonography of the renal tract is often added as the symptoms of bladder and renal cancer overlap.[6] For patients with bladder cancer, staging might require computerised tomography and isotope bone scanning; positron emission tomography is increasingly used in specialist centres.

How is it managed?

Initial treatment depends on staging; less advanced disease is resected transurethrally (TURBT). Patients with low risk disease are offered cystoscopic surveillance, while recurrent low risk disease or intermediate/high risk disease can require intravesical chemotherapy or immunotherapy (with BCG). More advanced disease can require cystectomy or radical radiotherapy, with or without neo-adjuvant chemotherapy.[2]

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Key points

- Women with bladder cancer are more likely to present with muscle invasive disease, partly associated with delays in diagnosis in primary care
- Haematuria is the most highly predictive symptom of bladder cancer, and appropriate investigation and referral should not be delayed
- If women are treated for presumed urinary tract infection, active follow-up should ensure that symptoms have settled with treatment with antibiotics
- Symptomatic women aged over 50 without confirmation of infection on urinalysis or microscopy and culture should be referred for further assessment to identify a definitive cause

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